54.(Twice Amended) A process for the production of biologically active VEGF-B, said method comprising expressing a nucleic acid molecule which hybridizes under high stringency conditions to a full-length reverse complement of a nucleic acid of SEQ ID NO:9 in a host and isolating said VEGF-B, wherein said high stringency conditions comprise 0.1-1X SSC/0.1% w/v SDS at 60°C for 1-3 hours.

REMARKS

In the Office Action dated August 29, 2002, claims 26-28, 30, 46-49 and 56-58 are allowed. Claims 50-55 have been rejected under 35 U.S.C. §112, first paragraph as allegedly lacking enabling support.

This response addresses the Examiner's rejection. Accordingly, the present application is in condition for allowance. Favorable reconsideration of all pending claims is therefore respectfully requested.

Claims 50-55 have been rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enabling support. The Examiner admits that the specification is enabling for "making biologically active VEGF-B by expressing a nucleic acid molecule of SEQ ID NOS:3,5,7 or 9". The Examiner alleges that the claims encompass "any nucleic acid which hybridizes and would make biologically active VEGF-B". The Examiner further alleges that claims "encompass small pieces of DNA, since they would hybridize DNA which has mutations which would alter the coding sequence which could also hybridize, and DNA which may encode other VEGF molecules other than VEGF-B".

Applicants respectfully submit that the pending claims, as amended, are fully enabled by the present specification, in compliance with the requirements of 35 U.S.C. §112, first

paragraph. Support for the amendments to claims 50-54 is found throughout the specification and particularly at page 6, line 28 through page 7, line 2, for example. No new matter has been added. Applicants respectfully submit that the skilled artisan would readily understand that only a full-length cDNA would produce biologically active VEGF-B, thereby effectively mooting the Examiner's contention that the claims encompass "small pieces of DNA". Nevertheless, Applicants have amended the claims in an effort to expedite favorable prosecution.

The Examiner alleges that "the claims encompass DNA which has mutations which would alter the coding sequence, which would also hybridize and DNA which may encode other VEGF molecules other than VEGF-B". Applicants respectfully submit that claims 50-55 are directed to nucleic acids with subtle variations of those listed in the examples, namely cDNA's that carry variations in the 3' or 5' untranslated regions, or any variation in the coding region if and only if such variation does not alter the biological activity of VEGF-B, since such variant nucleic acids would hybridize under high stringency conditions and would yield a biologically active VEGF-B. Moreover, Applicants submit that the claims fully characterize the stringency conditions which permit the production of biologically active VEGF-B. In this regard, Applicants submit that only a very limited number of sequences would hybridize under the claimed stringency conditions. Notably, the claims have been amended to obviate the contention that shorter hybridizing sequences are even contemplated.

The Examiner alleges that it would require undue experimentation to practice the instant invention because "it is not predictable which of those nucleic molecules which hybridize will also encode biologically active VEGF-B". Applicants respectfully submit that the Examiner's position appears to impute a level of predictability and a low level of skill in the art, which simply did not exist at the time the present application was filed. Clearly, some

experimentation is not only permissible, but expressly sanctioned under the law. Some experimentation would naturally be required to generate recombinant fragments of VEGF-B (i.e. using the method of claims 50-55, selecting nucleic acids that hybridize under high stringency conditions) and testing fragments for VEGF-B-like biological activity (e.g. using any one of the VEGF-B-activity assays described in the present application). This is true, even more so, for full-length VEGF-B molecules. Thus, while experimentation is required to make and use the invention, such experimentation is certainly not undue.

Successful practice of the claimed invention does not require undue experimentation because of the high level of skill in the art and the availability of all the methods required to practice the invention, at the relevant date. The skills required to express VEGF-B molecules were available well before the priority date of the claims. See, for example, U.S. Patent No. 5,332,671, assigned the Genentech, Inc. which describes the expression and activity of recombinant VEGF. Also, cited in the instant application, see Sambrook J. et al. (1989) which on page 17.30 describes expression of fusion proteins, on page 17.32 describes expression of secreted proteins, and on page 17.38 describes the isolation of expressed proteins from inclusion bodies.

Furthermore, Applicants request reconsideration of the pending claims in view of the explicit direction and guidance provided in the specification and particularly in view of Examples 4 and 7 of the application which provide a range of assays to test the activity of expressed VEGF-B molecules.

Accordingly, the rejection of claims 50-55 under 35 U.S.C. §112, first paragraph is overcome and withdrawal thereof is respectfully requested.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

Thus, the present application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claims 50-54 have been amended as follows:

50.(Twice Amended) A process for the production of biologically active VEGF-B, said method comprising expressing a nucleic acid molecule which hybridizes under high stringency conditions to a full-length reverse complement of a nucleic acid of SEQ ID NOS: 3, 5, 7 and 9 in a host and isolating said VEGF-B, wherein said high stringency conditions comprise 0.1-1X SSC/0.1% w/v SDS at 60°C for 1-3 hours.

51.(Twice Amended) A process for the production of biologically active VEGF-B, said method comprising expressing a nucleic acid molecule which hybridizes under high stringency conditions to a full-length reverse complement of a nucleic acid of SEQ ID NO:3 in a host and isolating said VEGF-B, wherein said high stringency conditions comprise 0.1-1X SSC/0.1% w/v SDS at 60°C for 1-3 hours.

52.(Twice Amended) A process for the production of biologically active VEGF-B, said method comprising expressing a nucleic acid molecule which hybridizes under high stringency conditions to a full-length reverse complement of a nucleic acid of SEQ ID NO:5 in a host and isolating said VEGF-B, wherein said high stringency conditions comprise 0.1-1X SSC/0.1% w/v SDS at 60°C for 1-3 hours.

53.(Twice Amended) A process for the production of biologically active VEGF-B, said method comprising expressing a nucleic acid molecule which hybridizes under high stringency conditions to a full-length reverse complement of a nucleic acid of SEQ ID NO:7 in a host and isolating said VEGF-B, wherein said high stringency conditions comprise 0.1-1X SSC/0.1% w/v SDS at 60°C for 1-3 hours.

54.(Twice Amended) A process for the production of biologically active VEGF-B, said method comprising expressing a nucleic acid molecule which hybridizes under high stringency conditions to a full-length reverse complement of a nucleic acid of SEQ ID NO:9 in a host and isolating said VEGF-B, wherein said high stringency conditions comprise 0.1-1X SSC/0.1% w/v SDS at 60°C for 1-3 hours.